

**Nos. 14-1361, -1366**

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**United States Court of Appeals  
For The Federal Circuit**

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**IN RE BRCA1- AND BRCA2- BASED HEREDITARY  
CANCER TEST PATENT LITIGATION**

UNIVERSITY OF UTAH RESEARCH FOUNDATION,  
THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA,  
HSC RESEARCH AND DEVELOPMENT LIMITED PARTNERSHIP,  
ENDORECHERCHE, INC., AND MYRIAD GENETICS, INC.,

*Plaintiffs-Appellants,*

v.

AMBRY GENETICS CORPORATION,  
*Defendant-Appellee.*

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Appeal from the United States District Court for the Central District of Utah  
in consolidated case no. 2:13-cv-00640,  
Judge Robert J. Shelby.

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**APPELLANTS' REPLY BRIEF**

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**CERTIFICATE OF INTEREST**

Counsel for the Plaintiff-Appellant, Myriad Genetics, Inc. certifies the following:

1. The full name of every party or amicus represented by me is:

Myriad Genetics, Inc.

2. The name of the real party in interest represented by me is:

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3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

None.

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**CERTIFICATE OF INTEREST**

Counsel for the Plaintiffs-Appellants, University of Utah Research Foundation, The Trustees of the University of Pennsylvania, HSC Research and Development Limited Partnership, Endorecherche, Inc., and Myriad Genetics, Inc. certifies the following:

1. The full name of every party or amicus represented by me is:

University of Utah Research Foundation, The Trustees of the University of Pennsylvania, HSC Research and Development Limited Partnership, Endorecherche, Inc., and Myriad Genetics, Inc.

2. The name of the real party in interest represented by me is:

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3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

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## INTRODUCTION

Unwilling to defend the district court’s section 101 analysis in the first instance, Ambry instead elevates to the focal point of this appeal a mistake on a patent expiration date made by all parties before the district court. But the five-month mistake on the earliest expiration date of the patents-in-suit is just that—a mistake. It is not a “misrepresentation,” as Ambry loudly trumpets. Nor does it change the proper outcome of this appeal—it was not material to the district court’s irreparable harm analysis and it is not material to this appeal.

Substantively, Ambry does nothing to support the district court’s erroneous finding on patent eligibility under section 101. On the method claims, Ambry continues to brush aside the fact that claims 7 and 8 of the ’441 patent are nearly identical to claim 21, which both Judge Bryson and the Supreme Court in *AMP* suggested is patent eligible. Although not a “holding” that binds this Court, there can be no doubt that Judge Bryson’s and the Supreme Court’s comments are persuasive and should not be ignored, as the district court did. Ambry also continues to ignore the district court’s fatal error in failing to evaluate the claims as a whole. Contrary to *Diehr*, the district court found that claims 7 and 8 have no inventive concept “aside from” the BRCA1 sequence, but never evaluated at whether the combinations of steps in the claims *with* the BRCA1 sequence contained an inventive concept. Under the proper analysis, they do, just like the

claims found eligible in *Diehr*.

On the primer-pair claims, Ambry carries on the charade that the Supreme Court determined in *AMP* that primers and probes are ineligible subject matter. This Court should roundly reject such a characterization and clarify for the biotechnology patent community the true scope of that decision. *AMP* did not decide the patentability of primers or probes because the invalidated claims were not limited to primers or probes, as acknowledged by petitioners in that case, who are Ambry's amici here. Unlike the claims at issue in *AMP*, claims 16 and 17 of the '282 patent are expressly limited to primer pairs, creations of man that have a utility very different than natural DNA.

On irreparable harm, Ambry does not challenge the district court's findings based on the evidence that is actually in the record, but puts forward new "evidence" that was not before the district court. This is improper and should be rejected. But even if it were properly before this Court, Ambry's new evidence does not show any error. Rather, the facts show that Myriad's reimbursements have been reduced and third parties have terminated their contracts with Myriad since the district court's ruling.

The district court's refusal to enter a preliminary injunction based on its section 101 analysis was erroneous and should be reversed.

## I. THERE IS NO SUBSTANTIAL QUESTION OF PATENT ELIGIBILITY ON THE METHOD CLAIMS

### A. Ambry Continues to Ignore that the Supreme Court Suggested that Claims Nearly Identical to Claims 7 and 8 Are Patentable

As the district court did before it, Ambry continues to ignore the striking similarity between claims 7 and 8 of the '441 patent and claim 21—a claim that Judge Bryson indicated would be patent eligible. As shown in Myriad's opening brief, the language of claim 7 of the '441 patent and claim 21 of the '441 patent is nearly identical. [Opening Br. at 17.] Both contain the steps of hybridizing a BRCA1 gene probe and detecting the presence of a hybridization product. And claim 8, instead of reciting probe-based hybridization, recites primer-based amplification and sequencing, specific physical steps that have the same effect for purposes of section 101. Ambry cannot avoid the weight of Judge Bryson's statements by pointing out that claim 21 requires the probe to hybridize to "RNA," whereas claim 7 requires the probe to hybridize to "genomic DNA." [Ambry Br. at 48.] For purposes of evaluating patent eligibility of a method under section 101, there is no practical difference between hybridizing to RNA versus DNA.

And while Myriad does not argue that there is any *holding* from *AMP* that claim 21 of the '441 patent is patentable, Judge Bryson's guidance is persuasive and should not simply be ignored. Indeed, the Supreme Court found it persuasive enough to cite it favorably in *AMP*, explaining that "Judge Bryson aptly noted that,

‘as the first party with knowledge of the [BRCA1 and BRCA2] sequences, Myriad was in an excellent position to claim applications of that knowledge. Many of its unchallenged claims are limited to such applications.’’’ *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2120 (2013) (“AMP”). If Judge Bryson was correct that claim 21 is patentable, which the Supreme Court appeared to believe, then claims 7 and 8 are similarly patentable.

**B. Claims 7 and 8 of the ’441 Patent, Viewed as a Whole, Contain an Inventive Concept**

But even putting aside the weight to be given them, Judge Bryson’s views, provided *after* the *Mayo* decision, are well-supported under the law. Ambry continues to miss the point that the “inventive concept” that the Supreme Court has discussed under section 101 must be judged by looking at the claims *as a whole*, not by first excising any reference to a natural law. The issue is thus not whether probe-based hybridization and detection and primer-based amplification and sequencing had been performed before in other contexts, with other DNA sequences. The issue is whether an inventive concept exists in the context of the entire claim—including both the natural law and the other steps. *See Ultramercial, Inc. v. Hulu, LLC*, 722 F.3d 1335, 1344 (Fed. Cir. 2013).

The requirement that the claims be viewed as a whole can be traced back at least to *Diamond v. Diehr*, 450 U.S. 175, 189 (1981), which held that, “[i]n determining the eligibility of respondents’ claimed process for patent protection

under § 101, their claims must be considered *as a whole*. It is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis.” The Court explicitly reversed the contrary holding from *Parker v. Flook*, 437 U.S. 584 (1978), on this very point. *Diehr*, 450 U.S. at 189 n.12. While it asserts that the district court did not violate this rule, Ambry’s citations to the district court opinion demonstrate the contrary. The district court found that “[t]he claims contain **no otherwise new process** for designing or using probes, primers, or arrays beyond the use of BRCA1 and BRCA2 sequences in those processes,” and that “[a]side from the patent ineligible, naturally occurring nucleotide sequence of the BRCA1 and BRCA2 genes,” the other steps in the claims recite routine and conventional activity. [A93-94 (emphasis added).] This is all contrary to the directive in *Diehr* not to dissect the claims.

Claims 7 and 8 of the ’441 patent are patent eligible under section 101 for the same reasons as the claims found patentable in *Diehr*. In *Diehr*, although each of the claimed steps—placing rubber in a mold, measuring a temperature, performing calculations, and opening the rubber mold—had been done before in different contexts, the overall method was patentable because the combination of steps for the claimed purpose represented a new “application of a law of nature or mathematical formula to a known structure or process.” 450 U.S. at 178-79. As the Supreme Court explained in *Mayo*, “[*Diehr*] nowhere suggested that all these

steps, or at least the combination of steps, were *in context* obvious, already in use, or purely conventional.” *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1299 (2012) (emphasis added).

The same is true here. The asserted claims recite a new combination of steps for a new, specific purpose—the assessment of risk for deadly diseases—and are patentable applications using the knowledge of a natural DNA sequence. The BRCA1 gene sequence was unknown before Myriad’s discovery, and Myriad had to design the probes and primers used in the steps of claims 7 and 8. [Opening Br. at 34; A9144-46.] Although the hybridization and amplification steps had been done before in other contexts, with other genes, Myriad was the first to make the application to the BRCA1 sequence. This Court has characterized an “inventive concept” as “a genuine human contribution to the claimed subject matter” or “a product of human ingenuity,” and there can be no doubt that claims 7 and 8 meet this standard. *CLS Bank Int’l v. Alice Corp.*, 717 F.3d 1269, 1283 (Fed. Cir. 2013).

Ambry improperly suggests that the Supreme Court in *AMP* has already found that Myriad “created no ‘innovative methods’” related to the BRCA1 gene. [Ambry Br. at 43.] But the quote that Ambry relies on relates specifically to methods “for manipulating genes while searching for the BRCA1 and BRCA2 genes.” *AMP*, 133 S. Ct. at 2119-20. It does not refer to the methods of probe and

primer-based hybridization and amplification at issue here. These methods are innovative.

In this regard, Ambry's erroneous arguments that claims 7 and 8 are not patentable as reciting abstract ideas simply prove Myriad's points. [See Ambry Br. at 47.] This is not an abstract idea case; the claims plainly recite specific physical steps, unlike the invalidated method claims from *AMP* that recited only the abstract "comparing" of DNA sequences. Importantly, this does not mean that recitation of physical steps alone is sufficient to make a claim patent-eligible under section 101, nor has Myriad suggested this, as Ambry wrongly asserts. [Ambry Br. at 49.] Indeed, the claims in *Mayo* were invalid even though, on their face, they included the physical steps of administering and determining, because those steps were required to make any use of the correlations at all—they were inherent in using the method itself. The point here is that, in conducting its analysis, Ambry—like the district court—ignores that this Court distinguished claims that truly were abstract from claims that would actually apply the step of comparing the sequences with steps like "sequencing the DNA molecule." *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 689 F.3d 1303, 1334-45 (Fed. Cir. 2012) ("AMP"). Claims 7 and 8 have such steps and are not merely "abstract" ideas. They claim an inventive concept—the use of new, specific tools to provide new information about

a patient's risk of deadly diseases—and the district court's contrary conclusion was error.

**C. Claims 7 and 8 of the '441 Patent Do No Unlawfully Preempt the BRCA1 Gene or Its Sequence**

As Myriad explained in its opening brief, “preemption” is not the test for eligibility under section 101. “[T]he proper focus is not preemption per se, for some measure of preemption is intrinsic in the statutory right granted with every patent to exclude competitors, for a limited time, from practicing the claimed invention.” *CLS Bank*, 717 F.3d at 1281. Rather, the main concern is ensuring that claims are not “coextensive with a natural law, natural phenomenon, or abstract idea.” *Id.*

The claims at issue in *Mayo* were invalid because they were coextensive with a natural law, and the recited steps were prerequisites to use that law. “Anyone who wants to make use of the[] [natural] laws must first administer a thiopurine drug and measure the resulting metabolite concentrations, and so the combination amounts to nothing significantly more than an instruction to doctors to apply the applicable laws when treating their patients.” *Mayo*, 132 S. Ct. at 1298.

Claims 7 and 8 of the '441 patent, on the other hand, are not “coextensive” with the BRCA1 gene, but add specific limitations directed to probe-based methods of hybridizing and detecting (claim 7) and primer-based methods of

amplifying and sequencing (claim 8). They do not cover all possible methods of determining or using the BRCA1 sequence. [See Opening Br. at 39-41.]

Ambry is wrong that these specific limitations in claims 7 and 8 somehow do not qualify as “meaningful limitations.” [Ambry Br. at 54.] As an initial matter, the district court did not even apply the correct standard set forth by this Court in *Ultramercial*, but instead based its decision on its newly-created “most widely used means” test, which wrongly finds preemption if a claim covers what is currently the most widely used means of using a natural product. [A95.] Neither the district court nor Ambry can cite anything to support this “most widely used means” standard because there is nothing to support it. The standard actually set forth in *Ultramercial*, and advanced by Ambry now, provides that a claim is “not meaningfully limited if its purported limitations provide no real direction, cover all possible ways to achieve the provided result, or are overly generalized.” 722 F.3d at 1346. Under that standard, the question is not whether the claims cover a particular method that individuals would commonly use in employing a natural product or natural phenomenon, but whether they cover all possible methods for employing that natural product or phenomenon. There can be little question that claims 7 and 8 do not cover all possible methods for using the BRCA1 gene, but

instead only the specific primer and probe-based hybridization and amplification methods recited.<sup>1</sup>

First, the claims do **not** prohibit others from developing other methods to use and evaluate the BRCA genes. As Myriad demonstrated in its opening brief, to which Ambry fails to respond, a critical part of the preemption analysis is whether the claims foreclose others from using the natural product to further innovation. The Supreme Court found the claims in *Mayo* invalid because they “cover[ed] all processes that make use of the [natural] correlations after measuring metabolites, including later developed processes that measure metabolite levels in new ways.” *Mayo*, 132 S. Ct. at 1302. The claims at issue here do not share that problem because they do not foreclose a “future inventor, in the onward march of science” from discovering new ways of applying and using the BRCA genes. *O'Reilly v. Morse*, 56 U.S. 62, 113 (1854).

Second, claims 7 and 8 do not cover all methods for studying the BRCA1 gene that are already in use by scientists in the field, including gene expression profiles, untargeted single-molecule sequencing, and protein truncation testing. [A9152-54; A6652-54.] Ambry does not address these methods at all, other than to assert that Myriad did not provide a “complete evidentiary showing.” [Ambry

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<sup>1</sup> Ambry’s amici suggest that claims 7 and 8 pose a First Amendment problem. They plainly do not—they do not cover simply thinking about the BRCA1 gene, as amici suggest, but are limited to the performance of specific steps.

Br. at 55.] But Ambry provided no showing at all to support its now-revised preemption claim. Ambry does nothing to suggest that these alternative technologies Myriad cited are not suitable alternatives for using the BRCA1 gene, and the district court did not consider this evidence at all. On appeal, Ambry merely argues that, because Myriad asserted claim 8 against Next Generation Sequencing (“NGS”) technology, one technology that did not exist at the time the patents were filed, the claims are impermissibly preemptive. [Ambry Br. at 55.] Ambry’s argument is without merit. The rule against preemption does not prohibit a claim from covering any future technology; it only prohibits it tying up all uses of a natural law. Even so, claim 8 does not cover all uses of NGS, but only those in conjunction with a PCR reaction using the claimed primer pairs.

Finally, none of the district court’s specific factual findings cited by Ambry [Ambry Br. at 51-52] actually supports Ambry’s argument. There is no finding that all the steps of the claims are **required** to isolate the BRCA1 gene for use and that the claims prohibit all possible ways of using the gene. Even the finding trumpeted by Ambry that “[t]o study a gene, geneticists generally must amplify a given DNA sample” does not show this—it speaks only in terms of what scientists generally do, and not what the claims say. [*Id.*] Indeed, rather than supporting Ambry’s arguments, this finding simply shows that the district court applied the

erroneous legal standard in its preemption analysis, and that the claims viewed properly do not unlawfully preempt anything.

## **II. MYRIAD DID NOT WAIVE ITS RIGHTS AS TO THE '155 PATENT**

To simplify the appeal, Myriad selected four claims as representative—two method claims and two primer pair claims. Ambry cites nothing to suggest that the selection of representative claims somehow waives the right to appeal on claims that those representative claims were explicitly stated to represent.

Myriad explained in its opening brief that claims 2 and 4 of the '155 patent “are similar to [representative] claims 7 and 8 of the '441 patent in that they employ primers to achieve their methods.” [Opening Br. at 19-20 n.3; A348; A140-41.] Indeed, in some ways, the '155 patent claims are even narrower than the '441 claims, with the '155 claims reciting the repetition of the primer amplification and sequencing steps and a determination of the presence or absence of particular polymorphic variations that correlate with genetic susceptibility to breast or ovarian cancer. [A348.] Ambry fails to articulate a reason why these claims would have a different result under section 101. Ambry suggests that the '155 claims are different because they require only a single primer rather than a probe or set of primers like the '441 claims, but fails to explain why that distinction is important in a method claim. As noted, Myriad pointed out the

similarities between the claims and why the analysis under section 101 should not be substantially different. There has been no waiver.

### **III. THERE IS NO SUBSTANTIAL QUESTION OF PATENT ELIGIBILITY OF THE PRIMER PAIR CLAIMS**

Ambry continues to improperly equate claims directed to “a pair of single-stranded DNA primers for determination of a nucleotide sequence of a BRCA1 gene by a polymerase chain reaction” with claims to “an isolated DNA.” They are not the same, and Ambry’s attempt to mislead this Court (as it did successfully below) should be rejected.

#### **A. The Supreme Court Did Not Decide the Patentability of Primer Pairs in *AMP* or Hold that All “Isolated” DNA Fragments, However Claimed or Used, Are Patent Ineligible**

Ambry’s repeated assertion that the Supreme Court held in *AMP* that primers and probes are patent ineligible is demonstrably false.<sup>2</sup> [See Ambry Br. at 9, 10, 13.] The claims found invalid by the Supreme Court in *AMP* were broadly directed to an “isolated DNA” coding for a BRCA1 or BRCA2 protein, which encompasses both naturally occurring BRCA1/2 genomic DNA, as well as man-made products. As Judge Bryson noted, the problem with these claims was that

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<sup>2</sup> Similarly false are Ambry’s assertions that Myriad does not challenge any aspect of the district court’s fact-finding. This ignores large portions of Myriad’s opening brief explaining why the district court erred in not giving any weight to the meaningful differences in composition and utility between the claimed primer pairs and a natural DNA fragment, which were largely undisputed by the parties. [See Opening Br. at 50-54.]

they were *not* limited to primers or probes. *AMP*, 689 F.3d at 1356.

Despite going on for pages trying to equate claims directed to “a pair of single-stranded DNA primers for determination of a nucleotide sequence of a BRCA1 gene by a polymerase chain reaction” with claims to “an isolated DNA,” Ambry knows that the two are not the same. As demonstrated in Myriad’s opening brief—and not even a matter of debate below (*see A14*)—primers and probes are made in the lab by scientists and used to perform a function that natural DNA fragments do not perform in nature: to prime synthesis of DNA in a PCR reaction. [Opening Br. at 48, 50-52.] Consistently, the claim language here—which Ambry does not once address—is directed to a man-made composition (“a pair of single-stranded DNA primers”) for use in a non-natural chemical reaction (“a polymerase chain reaction”). Plainly, these claims cover something far more specific than the “isolated DNA” claims found ineligible in *AMP*.

The Supreme Court itself understood that primers and probes were not at issue in *AMP*. As Myriad explained in its opening brief, Justice Sotomayor questioned petitioners in *AMP* to confirm that the primers and probes “would still stand”:

3 JUSTICE SOTOMAYOR: But the patent with  
4 respect to claims that are not invalid would still  
5 stand.

6 MR. HANSEN: That is correct, Your Honor.

7 JUSTICE SOTOMAYOR: The primers and probes  
8 stand.

9 MR. HANSEN: Would -- would still remain.

10 Even if you were to rule for Petitioners, you would not  
11 have to rule concerning the use of DNA as a probe or a  
12 primer.

*AMP*, Oral Argument Tr. (Apr. 15, 2013) at 11.<sup>3</sup> Ambry does not even address this colloquy in its brief.

Indeed, because they were not at issue, the words “primer” and “probe” are not even mentioned in the Supreme Court’s *AMP* decision. The Supreme Court found the claims broadly directed to isolated DNA unpatentable under section 101

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<sup>3</sup> Indeed, the record made clear that the *AMP* plaintiffs repeatedly stated that claims directed to primers and probes were not challenged. *See, e.g.*, Pls. Memorandum of Law in Support of Mt. for Summary Judgment at 14, *AMP*, Case No. 09 Civ. 4515 (S.D.N.Y. Jan. 20, 2010) (“In fact, defendants’ patents do indeed have claims directed just to use of isolated DNA segments as primers, but plaintiffs have not challenged any of those claims. . . . Plaintiffs have only challenged claims that have not been limited to DNA used as primers[.]”); Br. for Appellee at 15-16, *AMP*, Case No. 2010-1406 (Fed. Cir. I, Nov. 30, 2010) (“None of the claims at issue in this case is limited to the use of BRCA1/2 as a primer. Myriad has obtained such patents. Claim 16 of Patent ’282 is one such claim and is not challenged here. . . . The Court is thus not being asked to rule on the patentability of DNA as either primers or probes.”); Suppl. Br. for Appellees at 8, *AMP*, Case No. 2010-1406 (Fed. Cir. II, June 14, 2012) (“Plaintiffs did not challenge claims limited to the use of short segments of DNA as probes or primers.”).

not because they encompassed primer or probes or cDNA, or because any isolated DNA was unpatentable, but because the claims encompassed natural, genomic DNA and fragments thereof. *See* ~~AMP~~, 133 S. Ct. at 2120 (“We merely hold that genes and the information they encode are not patent eligible under § 101 simply because they have been isolated from the surrounding genetic material.”). When the claims were limited to BRCA1 and BRCA2 cDNA, the Court held that these claims were patentable under section 101, even though cDNA is also a form of “isolated DNA,” and the claims directed to BRCA1 and BRCA2 cDNA were in fact dependent from the broad “isolated DNA” claims found invalid by the Court. *Id.* at 2113, 2119.

Thus, contrary to Ambry’s representation, the Court in ~~AMP~~ did not hold all forms of isolated DNA patent ineligible, nor has Myriad “reversed course” from its position in that case. Primers are not patent ineligible simply because they may be considered an “isolated DNA.” The correct inquiry is whether claims expressly limited to a pair of DNA primers for use in a coordinated fashion in a PCR reaction are patentable under section 101. *See id.* at 2113. As explained in Myriad’s opening brief and further discussed below, they are.

**B. The Primer Pair Claims Are Patentable Under Section 101 Because They Are Limited to a Pair of DNA Primers For Use in PCR, With Both Distinct Composition and Utility From Anything Found in Nature**

There is no risk that the claims limited to a pair of DNA primers would give Myriad a monopoly on an individual's isolated natural DNA fragments because the claimed primer pairs are not isolated natural DNA fragments, and are markedly different from isolated natural DNA fragments in both composition and utility. These differences guarantee that a claim limited to a pair of single-stranded DNA primers for use in PCR will not cover isolated natural DNA fragments. Thus, the district court incorrectly decided that the primer pair claims were invalid under section 101 and Supreme Court precedent.

Myriad's opening brief explained why a pair of single-stranded DNA primers for use in a PCR reaction is not a product of nature, and have markedly different structural and functional properties than DNA fragments found in nature. [See Opening Br. at 48-54.] In response, Ambry does not dispute that the claimed primer pairs are designed and made by scientists in a lab, not snipped from nature. Instead, in an effort to turn the man-made primer pairs into products of nature, Ambry relies on two arguments already rejected by the Supreme Court in *AMP*: (1) that the primer pairs must be "natural products" if their sequences are dictated by the genomic DNA one intends to amplify; and (2) that the primer pairs do not have a markedly different function than natural DNA fragments because both pair

with complementary DNA strands according to the Watson-Crick principle. [See Ambry Br. at 26-27.] These arguments should be rejected again here.

First, in finding BRCA1 and BRCA2 cDNA patent eligible in *AMP*, the Supreme Court has already rejected Ambry's argument that anything "dictated by nature" must be a natural product. As the Court warned in that decision: "The rule against patents on naturally occurring things is not without limits," for "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas." *AMP*, 133 S. Ct. at 2116 (quoting *Mayo*, 132 S. Ct. at 1293). As a result, "too broad an interpretation of this exclusionary principle could eviscerate patent law." *Id.* Applying these principles, the Court found BRCA1 and BRCA2 cDNA patent eligible (*i.e.*, not a natural product) even though their nucleotide sequences might also be said to be "dictated by nature":

[Petitioners] nevertheless argue that cDNA is not patent eligible because "the nucleotide sequence of cDNA is dictated by nature, not by the lab technician." That may be so, but the lab technician unquestionably creates something new when cDNA is made.

*Id.* at 2119.

As with cDNA, lab technicians unquestionably "create something new" when they design and make a pair of primers not found anywhere in nature. As a result, even if the nucleotide sequences of those primer pairs were "dictated by nature" (though really, they are chosen by the lab technicians), this would not render the primer pairs patent ineligible based on *AMP*.

Second, there is no question that the claimed primer pairs do not have the same function as DNA found in nature. It is undisputed that the claimed primer pairs do something that no DNA fragment does in the human body: they prime the exponential synthesis of a target DNA in a man-made PCR reaction and in a coordinated fashion. This entirely separate, man-made utility is a characteristic of the claimed primer pairs that is markedly different from isolated natural DNA fragments, in addition to the structural differences discussed in Myriad's opening brief and undisputed by Ambry. [See Opening Br. at 50-52.]

Ambry makes a feeble attempt to equate a PCR reaction with DNA replication in a human body. As explained in detail in Myriad's opening brief, the two processes are different. [See Opening Br. at 7-8, 51-52.] Even Ambry admits that, during natural DNA replication, the unwound, single, contiguous genomic DNA strands become available as a template, not as primers, and the priming function is carried out by RNA primers, not the DNA strands. [Ambry Br. at 37-38.] Thus, contrary to what the district court found and what Ambry argues, during PCR, the primers do not "function similarly to genomic DNA undergoing replication in the human body" for purposes of a section 101 analysis. [See *id.* at 33 (citing A85).] Moreover, not only is RNA structurally different from DNA (see A11), an RNA primer is also created in an entirely different way in a human body

than a pair of DNA primers created by a scientist in a lab. [See Opening Br. at 51-52.] None of these facts are disputed by Ambry.

Invoking the “Watson-Crick” principle no less than 16 times in its brief, Ambry attempts to obfuscate the non-natural utility of the claimed DNA primers—*i.e.*, to **prime**—with the law of nature on which that utility depends. The Watson-Crick base-pairing rule is not a **function** or **utility** of the primer pairs, but the underlying principle that dictates how DNA strands pair with one another. Just like Newton’s law of gravity, which applies to all objects with mass, does not render all inventions requiring the use of gravity patent ineligible, the Watson-Crick principle does not preclude all DNA from being patented. Indeed, the Supreme Court held BRCA1 and BRCA2 cDNA patent eligible, even though it too, like all DNA, relies on the Watson-Crick principle for its utility.<sup>4</sup> *Id.* at 2119.

Based on the undisputed facts, the claimed pair of primers is much more like the new bacterium in *Diamond v. Chakrabarty*, 447 U.S. 175 (1981), than the mixture of bacteria in *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948). Unlike the mixed culture of naturally occurring bacteria in *Funk Brothers*, the claimed primer pairs are not a mere mixture of two natural products serving “the ends nature originally provided,” with “no enlargement of the range of their

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<sup>4</sup> Likewise, there is no dispute that PCR—which the district court acknowledged as an “invention” (see A17)—also “relies on Watson-Crick base pairing[.]” [Ambry Br. at 6.]

utility.” 333 U.S. at 131. It is undisputed that the pair of single-stranded DNA primers are designed and created by scientists (*see A14*; Ambry Br. at 5-6)—synthesized one nucleotide residue at a time, in fact—rather than snatched from nature, as the root-nodule bacteria strains selected by the patentee in *Funk Brothers* were. 333 U.S. at 131. Moreover, unlike the mixed bacteria species in *Funk Brothers*, where “[n]o species acquires a different use” and each “infects the same group of leguminous plants which it always infected,” *see id.*, here, the man-made DNA primer pairs take on a utility possessed by no naturally occurring DNA fragments—working together to prime a non-natural PCR reaction in order to exponentially amplify a targeted sequence of DNA. Like the bacterium found patent eligible in *Chakrabarty*, they are “a product of human ingenuity having a distinct name, character and use.” 447 U.S. at 309-10 (citation and internal quotation marks and brackets omitted); *id.* at 310 (“Here, by contrast, the patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility.”).

The primer-pair claims are thus readily differentiated from the broad claims at issue in *AMP* and *In re Roslin Institute*, -- F.3d --, 2014 WL 1814014, at \*1, \*6 (Fed. Cir. May 8, 2014), which Ambry fails even to discuss. Unlike the invalid “isolated DNA” claims in *AMP*, which encompassed genomic BRCA1 and BRCA2 DNA or fragments thereof, or the broad “live-born clone” claims in

*Roslin*, which did not “describe clones that have markedly different characteristics from the donor animals of which they are copies,” claims 16 and 17 of the ’282 patent do not give Myriad the exclusive right to use an individual’s isolated natural DNA fragments because they do not claim those fragments. *See AMP*, 133 S. Ct. at 2113; *Roslin*, 2014 WL 1814014, at \*1, \*6.<sup>5</sup>

**C. Myriad Did Not and Does Not Rely on an “Incorrect Test for Patent Eligibility”**

Ambry mischaracterizes Myriad’s argument and wrongly suggests that Myriad proposes a test for patent eligibility that would render a product of nature patent eligible. [Ambry Br. at 35.] Contrary to Ambry’s assertion, Myriad has never argued that “if *a product of nature* has a structure or utility altered from that which is observed in nature, then it is patent eligible.” [*Id.* (emphasis added)] What Myriad has consistently argued is that a product having markedly different structure or utility from any found in nature by definition is not a “product of nature,” but a product made by man, and claims *limited* to such a man-made product *cannot* be invalid under section 101. Myriad’s position is supported not

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<sup>5</sup> For the same reason, they do not run afoul of the hypothetical claim addressed in dicta in *AMP* covering the cDNA of a “very short” gene with no introns. *See AMP*, 133 S. Ct. at 2119. That hypothetical claim would potentially cover an isolated genomic DNA having the same sequence. Here, claims 16 and 17 simply do not cover isolated, short DNA fragments at all.

only by logic but also by Supreme Court precedent. *See Chakrabarty*, 447 U.S. at 309-10.

To the extent Ambry asserts that a distinction in utility is irrelevant to the “markedly different characteristics” inquiry, Ambry is wrong. [See Ambry Br. at 35-36.] In *Funk Brothers*, a mixed culture of naturally occurring strains of bacteria was found to be an unpatentable product of nature because “[t]he combination of species produces no new bacteria, no change in the six species of bacteria, and *no enlargement of the range of their utility.*” 333 U.S. at 131 (emphasis added). Conversely, in *Chakrabarty*, an oil-eating bacterium created by combining an existing species of bacteria with naturally occurring plasmids was found to be patent eligible because its oil-eating property was “possessed by no naturally occurring bacteria,” and it thus was “a product of human ingenuity having a distinctive name, character and *use.*” 447 U.S. at 305, 309-10 (emphasis added; internal quotation marks and brackets omitted); *see also AMP*, 133 S. Ct. at 2117 (“The *Chakrabarty* bacterium was new ‘with markedly different characteristics from any found in nature[]’ due to the additional plasmids and resultant ‘capacity for degrading oil.’”) (internal citation omitted). In *AMP*, the Court made no comment on the “utility” of BRCA1 and BRCA2 cDNA in finding them patent eligible, not because difference in utility was irrelevant to the “markedly different characteristics” inquiry, but because the Court did not need to engage in such

inquiry as the cDNA was “unquestionably” something new, created by man. 133 S. Ct. at 2119.

Here, the claimed primer pairs are not only unquestionably designed and created by scientists, but also markedly different in both composition and utility from isolated natural DNA fragments. They are patent eligible under section 101.

#### **IV. THE DISTRICT COURT’S FINDING OF IRREPARABLE HARM IS BASED ON SOUND FINDINGS THAT HOLD TRUE TODAY**

##### **A. The Five-Month Error on Expiration Dates was Not Material to the District Court’s Finding**

The five-month error Ambry uncovered in patent expiration dates both parties presented to the district court is harmless and does not “fatally infect” the district court’s irreparable harm analysis. As an initial matter, loss of patent exclusivity is but one of many considerations a court may use to evaluate irreparable harm, but, standing alone, it cannot support an injunction. *Robert Bosch LLC v. Pylon Mfg. Corp.*, 659 F.3d 1142, 1149 (Fed. Cir. 2011) (“While the patentee’s right to exclude alone cannot justify an injunction, it should not be ignored either.”). Here, the district court found that Myriad established a likelihood of irreparable harm because of the price erosion and lost sales Myriad would likely suffer absent an injunction. [A58-62.] Although the district court also considered Myriad’s loss of patent term exclusivity, the court did not fixate on a particular date of expiration as critical. [A65-66.] Rather, the district court

focused on Myriad's timely enforcement actions to defend its patents' exclusivity and correctly found that the harm from that loss of exclusivity "*bolster[ed]*" Myriad's showing of a likelihood of irreparable harm, rather than served as the sole basis underlying it. [A66 (emphasis added).] Any error in calculating Myriad's patent expiration dates provides no basis for finding an abuse of discretion.

Moreover, irreparable harm stemming from the loss of patent exclusivity caused by infringement may be found even where the patents-in-suit do not expire for years after the enforcement action was brought. *Pfizer, Inc. v. Teva Pharms., USA, Inc.*, 429 F.3d 1364, 1380-81 (Fed. Cir. 2005) (affirming finding of irreparable harm where patents did not expire for nearly two years after date of appellate decision on preliminary injunction). In fact, courts may consider the loss of patent exclusivity without reference to specific expiration dates. *See, e.g., Douglas Dynamics, LLC v. Buyers Prods. Co.*, 717 F.3d 1336, 1345 (Fed. Cir. 2013) (considering the impact of infringement on a patentee's exclusive rights in assessing irreparable harm); *see also Robert Bosch*, 659 F.3d at 1149.

Accordingly, the five-month error made by both parties below did not "fatally infect" the district court's analysis. That analysis was sound regardless, and is similar to that found sufficient in numerous cases before this Court.

**B. Ambry's Attempts to Supplement the Record Are Improper**

In its responsive brief, Ambry inappropriately tries to supplement the record on irreparable harm with statements and occurrences post-dating the district court's decision. Because "the record on appeal is generally limited to that which was before the district court," Ambry's effort should be rejected. *Moore U.S.A., Inc. v. Standard Register Co.*, 229 F.3d 1091, 1116 (Fed. Cir. 2000); *see also Sky Techs. LLC v. SAP AG*, 576 F.3d 1374, 1377 n.4 (Fed. Cir. 2009) (denying request to add evidence the district court did not consider); Fed. R. App. P. 10(a). This Court has repeatedly declined to take judicial notice of evidence not first presented to the district court, which is better situated to consider relevance and assess weight. *See, e.g., Juniper Networks, Inc. v. Shipley*, 395 F. App'x 713 (Fed. Cir. 2010) (non-precedential) (refusing to judicially notice an archived website presented for the first time on appeal, including because the district court did not have the opportunity to assess its relevance, weight, or contextual significance); *F & G Research, Inc. v. Patent Wireless Tech., Inc.*, No. 2007-1206, 2007 WL 2992480, at \*2 (Fed. Cir. Oct. 15, 2007) (non-precedential) (same). To consider this material now, and without the benefit of the district court's review, would wrongly convert this Court into the fact-finder. *Icicle Seafoods, Inc. v. Worthington*, 475 U.S. 709, 714 (1986) (explaining that appellate courts should not make factual findings on their own). Moreover, the substantive contents of the evidence Ambry

now cites—conference calls with investors and websites—do not present the type of facts for which judicial notice is typically appropriate. *See Fed. R. Evid. 201(b); Brodsky v. Yahoo! Inc.*, 630 F. Supp. 2d 1104, 1111 (N.D. Cal. 2009) (taking judicial notice of the date of a conference call but not of the substantive statements made therein).

But, even if this court were to consider this new “evidence” on the merits, it does not undermine the district court’s irreparable harm finding at all. To the contrary, Ambry’s new evidence reports that Myriad has in fact suffered market loss and price erosion. [Ambry Br. at 23.] That those occurrences may not have impacted Myriad’s bottom line to date to some arbitrary degree Ambry seeks to impose does not negate irreparable harm. *Robert Bosch*, 659 F.3d at 1152 (“[T]he fact that an infringer’s harm affects only a portion of a patentee’s business says nothing about whether that harm can be rectified.”).

Moreover, it should not be surprising that Ambry has carefully selected its new “evidence.” Ambry fails to report that Myriad is suffering serious price erosion, as shown by the Centers for Medicare and Medicare and Medicaid Services’ continued reduced reimbursement amounts. [See Ambry Br. at 24.] And since the district court’s decision, at least two insurance providers have terminated

their contracts with Myriad.<sup>6</sup> These are the exact types of harm that Myriad predicted would occur and that the district court concluded were irreparable. There is no basis to conclude otherwise in light of subsequent events. [A58-62.]

## **V. JUDICIAL ESTOPPEL DOES NOT APPLY TO MAKE THE '441 PATENT EXPIRE ON AUGUST 12, 2014**

Ambry's gambit to moot portions of this appeal by requesting that Myriad be judicially estopped from benefiting from the actual expiration date of the '441 patent—January 20, 2015—should be rejected. As noted above, this was a mistake made by all parties below. The '441 patent states on its face that it was filed on January 5, 1996. [A250.] However, a certificate of correction reveals that it was filed on June 7, 1995. [A350.] Because of the timing of the GATT treaty and the filing of a terminal disclaimer over another BRCA patent, the actual expiration date of the '441 patent is January 20, 2015. Before the district court, Myriad stated that its patents begin to expire in August 2014, mistakenly looking at the date on the face of the patent rather than the certificate of correction. Neither party caught the error.

This is no misrepresentation or lie, as Ambry would have it, but a simple

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<sup>6</sup>[https://services5.horizon-bcbsnj.com/eprise/main/horizon/content/homepage/GeneralMsgnew/gen\\_2014.5.27\\_09.58.35](https://services5.horizon-bcbsnj.com/eprise/main/horizon/content/homepage/GeneralMsgnew/gen_2014.5.27_09.58.35;);  
[https://providers.amerigroup.com/Public%20Documents/NYNY\\_HP\\_GeneticTesting.pdf](https://providers.amerigroup.com/Public%20Documents/NYNY_HP_GeneticTesting.pdf).

mistake. Application of judicial estoppel requires both a perception that a party misled the court and would gain an unfair advantage if estoppel were not applied. *Eastman v. Union Pac. R.R.*, 493 F.3d 1151, 1156 (10th Cir. 2007). Neither of those criteria is satisfied. The district court was not “misled.” All parties made a mistake that Ambry did not catch until now. And, as explained in Section IV.A, Myriad gained no unfair advantage because the expiration date mistake is not material to the district court’s irreparable harm finding. Put more succinctly, Ambry’s implication that the district court would not have found irreparable harm had it known that Myriad had five more months of patent term is not serious. Ambry’s argument on judicial estoppel should be rejected.

## CONCLUSION

For the reasons set forth above and in Myriad’s Opening Brief, the district court’s denial of a preliminary injunction was an abuse of discretion.

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Respectfully submitted,

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**CERTIFICATE OF SERVICE**

I hereby certify that I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Federal Circuit by using the appellate CM/ECF system on June 13, 2014:

**APPELLANTS' REPLY BRIEF**

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**CERTIFICATE OF COMPLIANCE**

The Reply Brief for Appellants complies with the type-volume limitation set forth in FRAP 32(a)(7)B). The relevant portions of Appellants' Reply Brief, including all footnotes, contain 6,906 words, as determined by Microsoft Word® 2010.

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